In accordance with 37 C.F.R. §1.121(c)(1), we enclose separate pag s h ad d "CLAIMS - Version showing changes made" in which all the changes to each of the foregoing claims made relative to the previous version of that claim are shown explicitly.

Please add following new claims 107 to 112:

107. (New) The polypeptide of claim 97 wherein the polypeptide oxidizes a retinoid.

108. (New) The polypeptide of claim 97 wherein the polypeptide hydroxylates a retinoid.

109. (New) The polypeptide of claim 99 wherein the polypeptide oxidizes a retinoid.

110. (New) The polypeptide of claim 99 wherein the polypeptide hydroxylates a retinoid.

111. (New) The polypeptide of claim 101 wherein the polypeptide oxidizes a retinoid.

112. (New) The polypeptide of claim 101 wherein the polypeptide hydroxylates a retinoid.

Please cancel claims 96 and 103.

REMARKS

Claims 83 to 95, 97 to 102, and 104 to 112 are pending in the application.

No new matter has been added by the amendments made herein, the nature of which amendments is described in greater detail below.

Specification

Applicants have carefully reviewed the specification and sequence identifiers have been assigned to sequences in all instances found where sequences are indicated in th description and claims.

All of the foregoing amendm nts to the description have been made to insert such sequence identifiers, save for the correction of the word "invention" on page 8 of the application as filed, as set out on the accompanying pages showing the changes made to the specification. Applicants note that the sequence listing identifiers are those contained in the Sequence Listing submitted in connection with parent application Serial No. 08/882,164 on or about September 3, 1999.

Claim Objections

Claims 83 to 94 and 97 to 102 were objected to under 37 C.F.R. § 1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 83 has been amended to include a protein sequence encoded by a sequence that hybridizes to a sequence which varies from a specifically recited sequence due to the degeneracy of the genetic code, and this element has been deleted from claim 84.

Claim 96 has been deleted and claims 97, 99 and 101 rewritten in independent form.

The Markush groupings of claims 83, 84, 90, and 91 have been rewritten.

Each of now independent claims 97, 99, and 101 is directed to a polypeptide which binds to an antibody elicited by a protein having a specific sequence wherein the antibody is elicited by an epitope located within an unconserved region of the protein sequence.

Applicants believe these amendments meet all of the objections to the claims.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 96 to 106 were rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled person that the inventors had possession of the invention at the tim the application was filed.

Firstly, Applicants note that claim 96 has b en deleted, and each of the remaining independent claims of this sort, as amended, claims 97, 99 and 101, requires the antibody to be elicited by an epitope located within an unconserved region of the specified protein.

As for Applicants' possession of the invention, the Examiner's attention is directed to the first paragraph on page 36 of the application where it is stated, "[h]ybridoma cells can be screened immunochemically for production of antibodies specifically reactive with the peptide, and monoclonal antibodies isolated." The specification goes on, in the last paragraph on page 36, to describe, "[t]he polyclonal, monoclonal or chimeric monoclonal antibodies can be used to detect the proteins of the invention, portions thereof or closely related isoforms in various biological materials, for example they can be used in an ELISA, radioimmunoassay or histochemical tests. Thus, the antibodies can be used to quantify the amount of a P450RAI protein of the invention, portions thereof or closely related isoforms in a sample in order to determine the role of P450RAI proteins in particular cellular events or pathological states. Using methods described hereinbefore, polyclonal, monoclonal antibodies, or chimeric monoclonal antibodies can be raised to nonconserved regions of P450RAI and used to distinguish a particular P450RAI from other proteins." Comparison of sequences is described in the specification as filed in the paragraph bridging pages 30 and 31 of the application as filed, where it is stated, "[i]t is possible to compare the zP450RAI, mP450RAI and hP450RAI sequences described above. Of the 492 amino acids of zP450RAI (SEQ ID NO:2), it is possible to align 334 amino acids with the 497 amino acids of hP450RAI (SEQ ID NO:4). See Figure 9. On this basis, there is about 68% homology between the human and fish proteins. The degree of homology between the two amino acid sequences is slightly greater towards the C-terminus than in the N-terminal region. It also appears as though nucleic acid sequences encoding the conserved sequence Met-Lys-Arg-Gln-Lys ..." In the last paragraph on page 35 of the application, antibody preparation is described: "[t]he protein of the invention, or portions thereof, can be used to prepare antibodies specific for the proteins. Antibodies can be prepared which bind to a distinct epitope in an unconserved region of a particular protein. An unconserved region of the protein is one which does not have substantial sequence homology to other proteins, for example other members of the P450 family of cytochromes. Conventional meth ds can be used to prepare th antibodies. For example, by using a peptid f a P450RAI protein, polyclonal antisera or monoclonal

antibodies can be mad using standard methods. As demonstrated in Exampl 16, a mammal, (e.g. a mouse, hamster, or rabbit) can be immunized with an immunogenic form of the peptide which elicits an antibody response in the mammal." (emphasis added)

The quoted passages clearly demonstrate that the Applicants were in possession of sequences related to those protein sequences precisely set out in the application that would bind to antibodies raised against nonconserved regions of those protein sequences. Applicants thus respectfully request withdrawal of the rejection of claims 96 to 106 (now claims 97 to 106) on these grounds.

Claims 83, 86 to 90 and 93 to 106 were rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled person that the inventors had possession of the claimed invention. In particular, it has been alleged that the claims, by including conservatively substituted variants, do nothing more than claim an enzyme by function.

Claims 96 to 106 (now claims 97 to 106) have been amended so as not to recite conservatively substituted variants. The amendments to these claims are described in greater detail below, but insofar as rejection of these claims on these grounds is concerned, Applicants believe this renders their rejection moot.

Applicants respectfully traverse the rejection of claims 83, 86 to 90, and 93 to 95 on these grounds. The subject matter of all of the claims is based on specifically disclosed sequences, and variants related thereto through hybridization of coding sequences under high stringency conditions and conservatively substituted amino acid variants of encoded sequences.

Conservative amino acid substitutions, those which do not destroy the activity of the protein, are described in the application by both reference to the literature and with specific examples. These are described on page 33, lines 11 to 27 of the application as filed, where it is stated, "that a variety of substitutions of amino acids is possible while preserving the structure responsible for retinoid metabolizing acitivity of the proteins disclosed her in. Conservativ substitutions are described in the patent literature, as for example, in United States Patent No. 5,264,558. It is thus xpected, for example,

that interchange among non-polar aliphatic n utral amino acids, glycine, alanine, proline, valine and isoleucine, would be possible. Likewise, substitutions among the polar aliphatic neutral amino acids, serine, threonine, methionine, asparagine and glutamine could possibly be made. Substitutions among the charged acidic amino acids, aspartic acid and glutamic acid, could probably be made, as could substitutions among the charged basic amino acids, lysine and arginine. Substitutions among the aromatic amino acids, including phenylalanine, histidine, tryptophan and tyrosine would also likely be possible. These sorts of substitutions and interchanges are well known to those skilled in the art. Other substitutions might well be possible. Of course, it would also be expected that the greater the percentage of homology, i.e., sequence similarity, of a variant protein with a naturally occurring protein, the greater the retention of metabolic activity..."

Applicants respectfully disagree with the contention that this amounts to a claim to any protein having the desired function, i.e., to any protein having any amino acid sequence but which has the desired function regardless of structure. Claim 83, for example, requires that a nucleic acid sequence which encodes the protein hybridize under stringent conditions to a molecule having a specific sequence or a degenerate variant of that specific nucleic acid sequence, and that the protein oxidize a retinoid. It is only conservatively substituted variants of these proteins that are claimed. The claim includes only those variant proteins in which an individual amino acid is substituted for another amino acid of protein known to have function, and which would be reasonably expected not to destroy the activity of the protein as a whole. While it is admitted there is no limitation on the number of such substitutions that might be made, any such substitution is clearly based on one of basic claimed structures (a protein encoded by sequence that hybridizes to SEQ ID NO:3, 5, etc.) and would be one that would be known to the skilled person.

Claims 83 and 90 have further been amended to require the claimed protein to be one "which oxidizes a retinoid" rather than one having the "ability to oxidize a retinoid."

Applicants thus respectfully request withdrawal of the rejection of claims 83, 86 to 90, and 93 to 95 on these grounds.

Claims 83, 86 to 90, and 93 to 95 have further b en rejected und r 35 U.S.C. § 112, first paragraph because the recited function encompasses any oxidizing activity with substrate specificity as broad as any retinoid. It has been alleged that the specification is insufficient to put the skilled person in possession of the claimed genus. Applicants respectfully traverse this rejection.

Applicants draw the Examiner's attention to Figures 4 and 10, depicting the products of oxidation reactions described in Examples 3 (zebrafish enzyme) and 5 (human enzyme).

Referring first to working Example 3, as stated on page 15, lines 10 to 11 of the application, "zP450RAI expression in COS-1 cells promoted the rapid conversion of RA into both lipid- and aqueous-soluble metabolites." This is evident in Figures 4(a) and 4(b), which are elution profiles of radioactively labelled, lipid soluble RA metabolites of control and zP450RAI-transfected cells. The profiles clearly demonstrate that zP450RAI produces significant amounts (relative to control) of aqueous soluble metabolites other than (more polar than) RA, 4-OH-RA and 4-oxo-RA. Applicants discuss this in Example 3 (page 15, lines 20-23), as follows: "It is possible that the aqueous-soluble radioactivity represents glucuronides of RA metabolites or glucuronides of RA itself. Rapid glucuronidation of 4- and 18-hydroxy-RA in mammalian cell extracts has been reported by others [Wouters, 1992; Takatsuka, 1996]." Applicants reasonably expect that P450RAI oxidizes the18 position of the β-ionone ring as well as the 4-position, and that P450RAI oxidizes retinol as well as RA (see page 3, lines 23-26).

Referring now to Example 5, Applicants describe on page 17 trials in which they examined the metabolism of radioactively labelled RA by hP450RAI-transfected COS cells. Results of these trials are shown in Figures 10(a), 10(b) and 10(c). All three panels of the figure show radioactive RA-derived metabolites not in the control. hP450RAI produced significant amounts of both aqueous and lipid soluble metabolites. Moreover, at least two unidentified metabolites (i.e., not 4-OH-RA or 4-oxo-RA) were produced. Applicants reasonably believe these to be other retinoid oxidation products.

In summary, Applicants have demonstrat d that the isolated proteins described in the examples of the applicati n have more than all-*trans* retinoic acid 4-hydroxylase activity

and respectfully submit that limitation of claimed protection to a protein having such activity, as suggested on page 5 of the outstanding action, would unduly narrow the scope of Applicants' protection beyond that to which Applicants are entitled. Withdrawal of the rejection of claims 83, 86 to 90, and 93 to 95 on these grounds is thus respectfully requested.

Claims 96 to 106 (now claims 97 to 106) have been separately rejected in the paragraph bridging page 5 and 6 of the outstanding action. As described above, claim 96 has been deleted and remaining claims have been amended to require that the antibody be elicited by an epitope located within an unconserved region of a specific protein. Applicants respectfully submit that it is completely routine and well within the capacity of the skilled person to determine whether a protein binds to an antibody, and thus falls within the scope of Applicants' claimed invention. As described above, the first paragraph on page 36 of the application states, "[h]ybridoma cells can be screened immunochemically for production of antibodies specifically reactive with the peptide, and monoclonal antibodies isolated." In the last paragraph on page 36, the application describes "[t]he polyclonal, monoclonal or chimeric monoclonal antibodies can be used to detect the proteins of the invention, portions thereof or closely related isoforms in various biological materials, for example they can be used in an ELISA, radioimmunoassay or histochemical tests. Thus, the antibodies can be used to quantify the amount of a P450RAI protein of the invention, portions thereof or closely related isoforms in a sample in order to determine the role of P450RAI proteins in particular cellular events or pathological states. Using methods described hereinbefore, polyclonal, monoclonal antibodies, or chimeric monoclonal antibodies can be raised to nonconserved regions of P450RAI and used to distinguish a particular P450RAI from other proteins." In the last paragraph on page 35 of the application, antibody preparation is described: "[t]he protein of the invention, or portions thereof, can be used to prepare antibodies specific for the proteins. Antibodies can be prepared which bind to a distinct epitope in an unconserved region of a particular protein. An unconserved region of the protein is one which does not have substantial sequence homology to other proteins, for example other members of the P450 family of cytochromes. Conventional methods can be used to prepare the antibodies. For example, by using a peptide of a P450RAI protein, polyclonal antisera or monoclonal antibodies can be made using standard methods. As demonstrated in Example 16, a mammal, (e.g. a mouse, hamster, or rabbit) can be immunized with an immunogenic

form of the peptide which elicits an antibody response in the mammal." Withdrawal of the rejection of claims 97 to 106 on these grounds is respectfully requested.

Claims 83 to 106 have been rejected in the second paragraph on page 6 of the outstanding action, insofar as they are directed to conservatively substituted variants, for lack of written description.

Applicants believe that the rejection of claims 96 to 106 (now claims 97 to 106) has been rendered moot by the amendments made to these claims, as explained above.

With respect to the rejection of claims 83 to 95 on these grounds, as discussed above, Applicants believe that it is well within the capacity of the skilled person to substitute amino acids and to determine whether enzymatic function of the protein is retained. Conservative substitutions were described as in the application as filed, as outlined above, as was an assay for retinoid oxidizing activity. See, for example, Example 3. Withdrawal of rejection of claims 83 to 95 on these grounds is respectfully requested.

Claims 83, 86 to 90, and 93 to 106 stand rejected under 35 U.S.C. § 112, first paragraph, for not enabling conservatively substituted amino acid variants of specific proteins disclosed in the application, or of retinoid oxidizing proteins having any substrate activity that is encoded by a nucleic acid sequence that hybridizes to a specifically disclosed sequence and conservatively substituted variants thereof, or polypeptides of unknown function that binds to an antibody specific for a protein encoded by SEQ ID NOs:3, 5 or 31.

The issue of limiting proteins having retinoid oxidizing activity to those having all-*trans* retinoic acid 4-hydroxylase activity is discussed above. Applicants believe they were in possession of proteins having such other activities, that the specification is enabling with respect to such proteins, and that they are thus entitled to a claim for a protein having retinoid oxidizing activity. As for conservatively substituted variants of antibody-binding proteins having no function, claims 96 to 106 (now claims 97 to 106) have been amended, as described above, to remove this limitation from the claims. This leaves the issue of claims that include conservatively substituted variants of a protein sequence encoded by a nucleic acid sequence that hybridizes under high stringency conditions to any one of a number of specific sequences and retains retinoid oxidizing

activity. The amino acid sequence and corresponding nucleic acid sequences are essentially interchangeable given current computer technology (i.e., that available in 1996), and given the limited number of conservative amino acid substitutions that it is possible to make, from a computer programming stand point, the determination of whether a particular sequence is within or without the claim is quite routine. The only possible experimentation required is that of hybridization under the high stringency conditions specified and determination of protein activity. To the extent that such testing might be required, it could hardly be considered non-routine or onerous. Applicant thus respectfully request withdrawal of this rejection.

Claims 96 to 106 (now claims 97 to 106) have been rejected in the second paragraph on page 9 of the outstanding action for being drawn to proteins with no function. It is within the general knowledge of the skilled person to know that a protein that can bind to an antibody can be used, for example, in a competitive assay, as a control, etc., in analyzing for the native protein. It is not required that the function of a product be stated in a claim. Withdrawal of the rejection of these claims on these grounds is thus respectfully requested.

It is stated in the third paragraph on page 9 of the outstanding action that the skilled person would require guidance as to how to use a polypeptide of the invention as claimed in claims 96 to 106 (now claims 97 to 106). Applicants submit that it is well within the ability of the skilled person, given a protein which binds an antibody, to use such protein as a control in an assay for the native protein. An assay in which the activity of a protein Applicants' invention is described, for example, in Example 3, of the application as filed. Withdrawal of the rejection of these claims on these grounds is thus respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 83 to 95 and 103 to 106 have been rejected for reciting "conservatively substituted variant thereof", and for use of the term "including" in connection with a Markush grouping.

Each of indep ndent claims 83, 90, and 91 has been amended to recite "a conservatively substituted amino acid variant of a said protein which oxidizes (or hydroxylates, as the case may be) a retinoid", as has been dependent claim 95.

Claims 103 to 106 no longer include this phraseology, rendering moot this rejection.

Claims containing Markush groupings have been amended, as described above, and no longer include the term "including".

Applicant thus respectfully requests withdrawal of the rejection of the claims on these grounds.

In view of the foregoing discussion, applicants respectfully request withdrawal of this rejection and reconsideration.

Rejection under 35 U.S.C. § 102

Claims 96 to 106 (now claims 97 to 106) were rejected under 35 U.S.C. § 102 as being anticipated by each of Vetter *et al.* and Shen *et al.*

Elements of claims 96 and 97 have been combined into newly independent claim 97. Claim 97 now requires a claimed polypeptide to bind to an antibody elicited by a protein having the amino acid sequence SEQ ID NO:2 wherein the antibody is elicited by an epitope located within a specified unconserved region of the protein. Likewise, each of newly independent claims 99 and 101 has a similar requirement, as do all claims dependent from any of claims 97, 99 and 101.

Since each claimed polypeptide is required to bind to an antibody elicited by an unconserved region of the claimed protein, and since there would be no expectation on the part of the skilled person that such antibody would bind to any protein disclosed in the cited references, none of the proteins in the cited references can reasonably be expected to fall within the scope of any of these claims.

Applicants thus resp ctfully request withdrawal f this rejecti n.

Double Patenting

The Examiner advised that 84 and 85 are so close in content to claims 91 and 92, respectively, that issuance of both pairs of claims would amount to double patenting. Applicant respectfully submits that the claims are substantively different in scope from one another. The first pair of claims is directed to a protein which oxidizes a retinoid, while the second pair of claims is directed to a protein which hydroxylates a retinoid. Hydroxylation is a particular type of oxidation, different from, for example, epoxidation.

Applicant respectfully submits that claims 84 and 85 are broader in scope than claims 91 and 92, respectively, and allowance of both should not give rise to an objection under 37 C.F.R. § 1.75.

Remaining matters

Claims 107 to 112 are new the application. These claims, dependent on claims 97, 99, and 101, are directed to polypeptides which bind to antibodies and have retinoid oxidizing activity, or hydroxylate a retinoid, as indicated in each of the claims. Consideration of these claims by the Examiner is respectfully requested.

A supplemental Information Disclosure Statement is being sent by courier today for delivery to the PTO on May 7, 2002.

In view of the foregoing, applicants respectfully submit that current claims 83 to 95, 97 to 102, and 104 to 112 are allowable, and request reconsideration and allowance of the application.

The above amendments should not be construed as an acquiescence to any of the outstanding rejections and are being made for the purpose of expediting prosecution. Applicants reserve the right to file the same or similar claims in this application or another application.

Please charge any fees that may be required to Deposit Account No. 02-2553.

If the Examiner has any questi ns concerning this response, would like to discuss th application, or intends to issue an unfavorable Final Action, she is invited to telephone Applicants' undersigned agent.

Yours very truly,

John C. Hunt
Registration No. 36,424

May 6, 2002
Date

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SPECIFICATION - Version sh wing changes made ***09/668,482; May 6, 2002***

Paragraph bridging pages 8 and 9:

In a more particular aspect, the **invention** **[Invetion]** includes a DNA molecule of one of the indicated sequences in which the DNA molecule includes the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)**, wherein x has a value of up to 5. This sequence is conserved in all three of the nucleotide sequences identified as having promoter activity, particularly where x is 5. Even more particularly, the invention includes such a DNA molecule in which the sequence TCTGASSAAGKTAAC **(SEQ ID NO:40)** occurs downstream from the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)**. Even more particularly, the sequence includes the sequence AATT between the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)** and the sequence TCTGASSAAGKTAAC **(SEQ ID NO:40)**, the AATT having been found immediately downstream of the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)**. It has been observed that there can be up to six nucleotides between the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)** and the sequence TCTGASSAAGKTAAC **(SEQ ID NO:40)**. There can also be the sequence CAATTAAAGA **(SEQ ID NO:41)** upstream of the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)**. In a particular aspect, the nucleotide sequence having promoter activity includes the sequence CAATTAAAGATGAACTTTGGGTGAACTAATT **(SEQ ID NO:42)** and the sequence TATAA. Particularly, the sequence TATAA is downstream of the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)**, and more particularly, the sequence TATAA is downstream of the sequence TCTGASSAAGKTAAC **(SEQ ID NO:40)** and it can be spaced up to about 55 nucleotides downstream from the sequence **[TGAACT(N)$_x$TGAACT]** **TGAACTNNNNNTGAACT, where "N" can be any nucleotide and there can be 0 to 5 N (SEQ ID NO:39)**.

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Paragraph (lines 32 to 34) on page 12:

Figure 15 shows promoter sequences of human, mouse and zebrafish P450RAI **(SEQ ID NOs:33, 34, and 35, respectively)**. The boxed regions show highly conserved regions while the arrows indicate spaced apart consensus sequences of RAREs.

First paragraph on page 15:

In order to facilitate cloning of the PCR products, several changes were made to the reactions. Primers which included EagI restriction endonuclease sites were used in the reamplification. Based on results obtained in the differential display analysis, the upstream 5'-TGCCAGTGGA-3' **(SEQ ID NO:26)** primer was replaced by 5'-GTAGCGGCCGCTGCCAGTGGA-3' (SEQ ID NO: 29) and the downstream poly-T primer, 5'-TTT TTT TTT TTT AG-3' **(SEQ ID NO:6)**, was replaced by 5'-GTAGCGGCCGCT_{12}-3' (SEQ ID NO:30). In addition, the reaction volume was increased to 40 µl, isotope was omitted and 20 as opposed to 40 cycles were performed. 5 µl aliquots of the PCR reactions were removed and the products were visualized by electrophoresis in a 1% agarose gel followed by ethidium bromide staining and UV illumination.

First paragraph on page 24:

Cloning of Zebrafish P450RAI promoter. An adult zebrafish genomic library (1.0 x 10^6 pfu) was screened with the full length cDNA corresponding to zP450RAI and positive plaques purified through secondary and tertiary screening. Lambda DNA corresponding to positive plaques was prepared, and the inserts from these clones were excised by restriction enzyme digestion with NotI and subcloned into the plasmid SK+ (Stratagene). Genomic clones were analyzed by restriction enzyme digestion using enzymes from the polylinker of SK+, followed by Southern blotting using an oligonucleotide (5'-GTAGCACGGATGGTG-3' **(SEQ ID NO:43)**) which hybridizes to the nucleotide sequence encoding the N-terminus of the zP450RAI cDNA to identify fragments f the genomic clones which encode the N-terminal region. A 772 base pair PstI fragment which hybridized with the oligonucleotide probe was purified, ligated into

the vector SK+ and sequenced using the Core Facility for Protein/DNA Chemistry at Queen's University, Kingston, Canada. Sequence analysis identified this clone as containing the putative initial methionine followed by 129 base pairs of coding sequence, plus 651 nucleotides upstream (5'). Within this 772 base pair fragment, a 402 base pair HindIII fragment was found to contain the putative retinoic acid response element (RARE). This fragment was subcloned into the pGL3B luciferase vector, in both the forward and reverse orientations, (Promega) for transient transfection analyses.

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83. (Once amended) An isolated protein **[having the ability to oxidize]** **which oxidizes** a retinoid and encoded by a nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2x SSC at 50°C, to **a polynucleotide having a [the]** nucleotide sequence **selected from the group of sequences** shown as: SEQ ID NO:3**; a sequence which varies from SEQ ID NO:3 in a coding region due to the degeneracy of the genetic code; [or]** SEQ ID NO:5**; a sequence which varies from SEQ ID NO:5 in a coding region due to the degeneracy of the genetic code; [or]** SEQ ID NO:31**; a sequence which varies from SEQ ID NO:31 in a coding region due to the degeneracy of the genetic code**, **or [including]** a conservatively substituted amino acid variant **[thereof]** **of a said protein which oxidizes a retinoid**.

84. (Once amended) The isolated protein of claim 83 in which the nucleic acid molecule comprises a nucleotide sequence **selected from the group of sequences** identified as SEQ ID NO:3**, a sequence which varies from SEQ ID NO:3 in a coding region due to the degeneracy of the genetic code, [or]** SEQ ID NO:5**, a sequence which varies from SEQ ID NO:5 in a coding region due to the degeneracy of the genetic code, [or]** SEQ ID NO:31**, and a sequence which varies from SEQ ID NO:31 in a coding region due to the degeneracy of the genetic code [, or which varies from SEQ ID NO:3 or SEQ ID NO:5 or SEQ ID NO:31 in a coding region due to the degeneracy of the genetic code]**.

85. (Once amended) The isolated protein of claim 83 in which the sequence of the nucleic acid molecule comprises a part of a human, fish or mouse genome **[, or variants therefrom due to the degeneracy of the genetic code]**.

89. (Once amended) The isolated protein of claim 83 in which the nucleic acid molecule encodes a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:32, and **[a]** conservatively substituted amino acid **[variant thereof]** **variants of SEQ ID NO:2, SEQ ID NO:4, and SEQ ID NO:32 which oxidizes a retinoid**.

90. (Once amended) An isolated protein **[having the ability to hydroxylate]** **whi h**

hydroxylates a retinoid at the 4-position of the ß-ionone ring and encoded by a nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2x SSC at 50°C, to **a nucleic acid molecule having a [the]** nucleotide sequence **selected from the group of sequences** shown as: SEQ ID NO:3**; a sequence which varies from SEQ ID NO:3 in a coding region due to the degeneracy of the genetic code; [or]** SEQ ID NO:5**; a sequence which varies from SEQ ID NO:5 in a coding region due to the degeneracy of the genetic code; [or]** SEQ ID NO:31**; a sequence which varies from SEQ ID NO:31 in a coding region due to the degeneracy of the genetic code, or [including]** a conservatively substituted amino acid variant **[thereof] of a said protein which hydroxylates a retinoid**.

91. (Once amended) The isolated protein of claim 90 in which the nucleic acid molecule comprises a nucleotide sequence **selected from the group of sequences** identified as SEQ ID NO:3**, [or]** SEQ ID NO:5**, and [or]** SEQ ID NO:31 **[, or which varies from SEQ ID NO:3 or SEQ ID NO:5 or SEQ ID NO:31 in a coding region due to the degeneracy of the genetic code]**.

92. (Once amended) The isolated protein of claim 90 in which the sequence of the nucleic acid molecule comprises a part of a human, fish or mouse genome **[, or variants therefrom due to the degeneracy of the genetic code]**.

95. (Once amended) The isolated protein of claim 90 in which the nucleic acid molecule encodes a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, **and** SEQ ID NO:32**, or [and]** a conservatively substituted amino acid variant **[thereof] of a said protein which hydroxylates a retinoid**.

97. (Once amended) **An isolated [The]** polypeptide **[of claim 96] which binds to an antibody elicited by a protein having the amino acid sequence SEQ ID NO:2** wherein the antibody is elicited by an epitope located within an unconserved region of the protein, the unconserved region consisting of amino acids 1 to 432 of SEQ ID NO:2.

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99. (Once amended) **An isolated** **[The]** polypeptide **[of claim 96]** **which binds to an antibody elicited by a protein having the amino acid sequence SEQ ID NO:4** wherein the antibody is elicited by an epitope located within an unconserved region of the protein, the unconserved region consisting of amino acids 1 to 436 of SEQ ID NO:4.

101. (Once amended) **An isolated** **[The]** polypeptide **[of claim 96]** **which binds to an antibody elicited by a protein having the amino acid sequence SEQ ID NO:32** wherein the antibody is elicited by an epitope located within an unconserved region of the protein, the unconserved region consisting of amino acids 1 to 436 of SEQ ID NO:32.

104. (Once amended) The polypeptide of claim 97 encoded by a nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2x SSC at 50°C, to the nucleotide sequence shown as SEQ ID NO:3 **[, including a conservatively substituted amino acid variant thereof]**.

105. (Once amended) The polypeptide of claim 99 encoded by a nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2x SSC at 50°C, to the nucleotide sequence shown as SEQ ID NO:5 **[, including a conservatively substituted amino acid variant thereof]**.

106. (Once amended) The polypeptide of claim 101 encoded by a nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2x SSC at 50°C, to the nucleotide sequence shown as SEQ ID NO:31 **[, including a conservatively substituted amino acid variant thereof]**.

* * * TRANSMISSION RESULT REPORT (MAY. 6. 2002 3:12PM) * * *

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Petkovich *et al.*
Serial No.:	09/668,482
Filing Date:	September 25, 2000
Title:	Retinoid Metabolizing Protein
Examiner:	Elizabeth Slobodyansky, Ph.D.
Art Unit:	1652
Atty's Docket No.:	57600/00035

The Commissioner of Patents and Trademarks
Washington, D.C. 20231
U.S.A.

CERTIFICATE OF FACSIMILE TRANSMISSION

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John C. Hunt (Registration No. 36,424) — May 31, 2002 Date

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John Hunt
Box 25, Commerce Court West
Toronto, Ontario, Canada
M5L 1A9

Thank you

Dear Sir:

I enclose a response previously submitted by fax on May 6, 2002.

Yours very truly,

May 31, 2002
Date

John C. Hunt
Registration No. 36,424

BLAKE, CASSELS & GRAYDON LLP
Box 25, Commerce Court West
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